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Ibuprofen for acute treatment of episodic tension-type headache in adults (Review)

Derry S, Wiffen PJ, Moore RA, Bendtsen L

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TABLE OF CONTENTS

[Intervention Review]

Ibuprofen for acute treatment of episodic tension-type headache in adults

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ABSTRACT

Background

Tension-type headache (TTH) affects about one person in five worldwide. It is divided into infrequent episodic TTH (fewer than one headache per month), frequent episodic TTH (1 to 14 headaches per month), and chronic TTH (15 headaches a month or more). Ibuprofen is one of a number of analgesics suggested for acute treatment of headaches in frequent episodic TTH.

Objectives

To assess the efficacy and safety of oral ibuprofen for treatment of acute episodic TTH in adults.

Search methods

We searched CENTRAL (*The Cochrane Library*), MEDLINE, EMBASE, and our own in-house database to January 2015. We sought unpublished studies by asking personal contacts and searching on-line clinical trial registers and manufacturers' websites.

Selection criteria

We included randomised, placebo-controlled studies (parallel-group or cross-over) using oral ibuprofen for symptomatic relief of an acute episode of TTH. Studies had to be prospective and include at least 10 participants per treatment arm.

Data collection and analysis

Two review authors independently assessed studies for inclusion, and extracted data. Numbers of participants achieving each outcome were used to calculate risk ratio (RR) and number needed to treat for an additional beneficial outcome (NNT) or number needed to treat for an additional harmful outcome (NNH) of oral ibuprofen compared to placebo for a range of outcomes, predominantly those recommended by the International Headache Society (IHS).

Main results

We included 12 studies, all of which enrolled adult participants with frequent episodic TTH. Nine used the IHS diagnostic criteria, but two used the older classification of the Ad Hoc Committee, and one did not describe diagnostic criteria but excluded participants with migraines. While 3094 people with TTH participated in these studies, the numbers available for any form of analysis were lower than this; placebo was taken by 733, standard ibuprofen 200 mg by 127, standard ibuprofen 400 mg by 892, and fast-acting ibuprofen 400 mg by 230. Participants had moderate or severe pain at the start of treatment. Other participants were either in studies not reporting outcomes we could analyse, or were given one of several active comparators in single studies.

For the IHS-preferred outcome of being pain free at 2 hours the NNT for ibuprofen 400 mg (all formulations) compared with placebo was 14 (95% confidence interval (CI), 8.4 to 47) in four studies, with no significant difference from placebo at 1 hour (moderate quality evidence). The NNT was 5.9 (4.2 to 9.5) for the global evaluation of 'very good' or 'excellent' in three studies (moderate quality evidence). No study reported the number of participants experiencing no worse than mild pain at 1 or 2 hours. The use of rescue medication was lower with ibuprofen 400 mg than with placebo, with the number needed to treat to prevent one event (NNTp) of 8.9 (5.6 to 21) in two studies (low quality evidence).

Adverse events were not different between ibuprofen 400 mg and placebo; RR 1.1 (0.64 to 1.7) (high-quality evidence). No serious adverse events were reported.

Authors' conclusions

Ibuprofen 400 mg provides an important benefit in terms of being pain free at 2 hours for a small number of people with frequent episodic tension-type headache who have an acute headache with moderate or severe initial pain. There is no information about the lesser benefit of no worse than mild pain at 2 hours.

PLAIN LANGUAGE SUMMARY

Oral ibuprofen for acute treatment of episodic tension-type headache in adults

Frequent episodic tension-type headache (TTH) means having between one and 14 headaches per month. The condition causes much disability, and stops people concentrating and working properly. When headaches occur the pain usually goes away over time.

Ibuprofen is a commonly-used painkiller available without prescription in most parts of the world. The usual dose is 400 mg taken by mouth.

We searched the literature in January 2015 and found 12 studies involved 3094 participants. Of these, about 1800 were included in comparisons between ibuprofen 400 mg and placebo. Others involved lower doses of ibuprofen, or different types of ibuprofen, or were in comparisons with other active drugs.

The outcome preferred by the International Headache Society (IHS) is being pain free after two hours. This outcome was reported by 23 in 100 people taking ibuprofen 400 mg, and in 16 out of 100 taking placebo. The result was statistically significant, but only 7 people (23 minus 16) in 100 benefited specifically because of ibuprofen 400 mg.

The IHS also suggests a range of other outcomes, but few were reported consistently enough for them to be used. People with pain value an outcome of having no worse than mild pain, but this was not reported by any study.

About 4 in 100 people taking ibuprofen 400 mg had an adverse event with ibuprofen, the same as with placebo. There were no serious adverse events.

There are questions about how studies in this type of headache are conducted. These questions involve the type of people chosen for the studies, and the outcomes reported. This limits the usefulness of the results, especially for people who just have an occasional headache.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Oral ibuprofen compared with placebo for episodic tension-type headache

Patient or population: Adults with episodic tension-type headache

Settings: Community

Intervention: Oral ibuprofen 400 mg

Comparison: Oral placebo

Outcomes	Probable outcome with intervention	Probable outcome with comparator	RR, NNT, NNTp, or NNH (95% CI)	No of studies, participants	Quality of the evidence (GRADE)	Comments
Pain free at 2 hours	230 in 1000	160 in 1000	RR 1.5 (1.2 to 2.0) NNT 14 (8.4 to 47)	4 studies 1052 participants	Moderate	Variable results between studies despite no apparent heterogeneity Modest effect size leaves magnitude of effect open to change with more trials
Pain free at 1 hour	63 in 1000	58 in 1000	RR 1.5 (0.8 to 2.9) NNT not calculated	3 studies 711 participants	Moderate	Variable results between studies despite no apparent heterogeneity Modest effect size leaves magnitude of effect open to change with more trials
Global evaluation 'very good' or 'excellent'	400 in 1000	230 in 1000	RR 1.7 (1.3 to 2.1) NNT 5.9 (4.2 to 9.5)	3 studies 739 participants	Moderate	Variable results between studies despite no apparent heterogeneity Modest effect size leaves magnitude of effect open to change with more trials
Use of rescue medication over 6 hours	150 in 1000	260 in 1000	RR 0.6 (0.4 to 0.8) NNTp 8.9 (5.6 to 21)	2 studies 589 participants	Low	Only two studies reported this outcome

Adverse events	41 in 1000	38 in 1000	RR 1.1 (0.6 to 1.7) NNH not calculated	8 studies 1645 participants	High	Consistent results between studies
Serious adverse events	None reported				Moderate	No events Upgraded because of consistent results with single dose ibuprofen in other clinical situations

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

CI: confidence interval; RR: risk ratio; NNT: number needed to treat; NNTp: number needed to prevent an event happening; NNH: number needed to harm

BACKGROUND

Headaches are a commonly reported problem in community-based surveys worldwide. The lifetime prevalence of headache is estimated to be greater than 90% (Steiner 2004), and the annual prevalence rate is estimated to be 46% in the general adult population (Stovner 2007). Variations in reported prevalence may result from differences in study design, population, inclusion or exclusion of cases of infrequent episodic tension-type headache (TTH), overlap with probable migraine, cultural and environmental differences, or even genetic factors (Sahler 2012). TTH is more common than migraine, a finding replicated across the world (Oshinaike 2014; Vos 2012).

The management of people with headaches is, however, largely neglected, and may be fragmented by the involvement of clinicians from different medical specialities (neurology; ear, nose and throat; ophthalmology; psychiatry) (Rasmussen 2001). Because headache is rarely life-threatening and headache pain is generally mild to moderate in intensity, people often self medicate and do not seek formal care from health services (Rasmussen 2001).

Headache can be either primary or secondary (due to other systemic or local causes) (Green 2009). TTH belongs to the group of primary headaches and is seen in nearly one-third of those suffering from headaches; the large number of people affected imposes a significant burden on the healthcare system (Stovner 2007). Generally, episodes of TTH are mild to moderate in intensity and self limiting, but in a small group of people they may be more severe and disabling (Green 2009). People with longer-lasting or more severe headaches may seek help in a clinical setting, but the majority of people do not do so, resulting in inadequate and inappropriate management (Kernick 2008). In a community-based telephone survey to determine the medication patterns of 274 frequent headache sufferers, only 1% used prescription medication. The majority of people with headaches reported using over-the-counter (OTC) analgesics (56% using paracetamol (acetaminophen) and 15% aspirin), and the perceived effectiveness of OTC medication was approximately 7 on a scale of 0 to 10 (Forward 1998).

Strategies for the management of TTH used to be extrapolated from those applied for migraine. The World Health Organization (WHO) essential drug list, for example, does not include indications for the management of TTH (WHO 2007). In 2010, both the British Association for the Study of Headache (BASH) and the European Federation of Neurological Societies (EFNS) updated or published guidelines for the management of TTH (BASH 2010; Bendtsen 2010); there is also German and Austrian guidance (Haag 2011). The guidelines reflect ongoing systematic efforts to bridge the gap between clinical trial evidence and clinical practice with the aim of improving practice.

People with TTH have more work absence than people with migraine or people without headaches (Lyngberg 2005); there is also considerable loss of productivity (Cristofolini 2008; Pop 2002). Headache-related characteristics include significant problems with headache management, disability, pain, worry and dissatisfaction with care, as well as greater use of medical services and worse general health (Harpole 2005).

Description of the condition

Tension-type headache (TTH) is known by several names, including tension headache, muscle contraction headache, psychomyogenic headache, stress headache, ordinary headache, essential headache, idiopathic headache, and psychogenic headache (IHS 2013). TTH is diagnosed mainly by the absence of features found in other headache types, especially migraine. The third edition of the International Classification of Headache Disorders (ICHD-3 beta) separates TTH into episodic and chronic varieties (IHS 2013). Chronic TTH is diagnosed when headache occurs on 15 days or more per month on average, for 3 months or more (180 or more days per year); otherwise TTH is considered to be episodic.

Acute treatment with analgesics is more appropriate for episodic TTH, while both pharmacological and non-pharmacological treatments are used for managing chronic TTH. Structural changes in the brain have been reported in chronic TTH (Schmidt-Wilcke 2005). Further, management of TTH in children and adolescents poses a clinically diverse situation (establishing diagnoses, dosages, nature of preparation, pharmacodynamics) (Monteith 2010). For all these reasons, the proposed review will focus on the acute treatment of episodic TTH in adults.

Diagnosis

Episodic TTH is subdivided into infrequent and frequent types (IHS 2013).

Infrequent episodic TTH is defined by the following criteria.

1. At least 10 episodes occurring on less than 1 day per month (fewer than 12 days per year) and satisfying criteria 2 through 4.
2. Headache lasting from 30 minutes to 7 days.
3. Headache has at least two of the following characteristics.
   a. bilateral location.
   b. pressing or tightening (non-pulsating) quality.
   c. mild or moderate intensity.
   d. not aggravated by routine physical activity such as walking or climbing stairs.
4. Both of the following.
   a. no nausea or vomiting (anorexia may occur).
   b. no more than one of photophobia or phonophobia.
5. Not better accounted for by another International Classification of Headache Disorders (ICHD-3 beta) diagnosis.

Frequent episodic TTH is defined as at least 10 episodes of headache occurring on at least 1 day but fewer than 15 days per month for at least three months (at least 12 and fewer than 180 days per year), and when criteria 2 through 5, above, are also met.

Prevalence

The one-year prevalence of infrequent episodic TTH in a Danish study of 4000 people aged 40 years was 48%, while that for frequent episodic TTH was 34% (Russell 2005). The overall annual prevalence of TTH in the United States was estimated to be 38%, with a higher incidence among women (prevalence ratio of 1.2 (Schwartz 1998)). In Canada, the prevalence was 29% (Edmeads 1993). A study conducted in Chile reported that TTH constituted 72% of all recurrent headaches, with a prevalence of 27% (95% confidence interval (CI), 25 to 29). Nearly one-quarter (24%) had

episodic TTH, and the prevalence was greater amongst women than men (35% versus 18%) (Lavados 1998).

The global prevalence of TTH was given as 21% in the Global Burden of Diseases Study 2010, making it the second most prevalent condition after dental caries, and slightly more prevalent than migraine (Vos 2012).

Causation

The exact pathogenesis of TTH is still unknown and is said to be multifactorial, including central dysfunction of pain-processing pathways and peripheral myofascial factors. There is a general agreement that peripheral myofascial nociception disturbances have a role in the pathogenesis of both frequent and infrequent episodic TTH (Fernández-de-Las-Peñas 2010; Fumal 2008).

Description of the intervention

Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and antipyretic properties. Ibuprofen was developed in the 1960s and is used extensively throughout the world for relief of pain and inflammation in both acute and chronic conditions. It is available OTC in most countries, usually as 200 mg tablets, with 1200 mg as the recommended maximum daily dose for adults. Under medical supervision, up to 3200 mg daily may be taken in divided doses, though the usual prescribed dose is up to 2400 mg. Ibuprofen salts (arginine, lysine, sodium) and some other fast-acting formulations are known to be more effective than standard acid formulations in treating acute postoperative pain, largely because of earlier absorption and higher plasma concentrations (Moore 2014a, Moore 2015).

Ibuprofen has been widely used in treating arthritis, dental pain, menstrual cramps, and a variety of other acute pain conditions; the usual recommended adult dose for acute pain is 400 mg up to three times daily. OTC medications are less expensive, more accessible, and have favourable safety profiles relative to many prescription treatments. Ibuprofen is effective for migraine headache treatment (Rabbie 2013), and the success rate with ibuprofen 400 mg in obtaining a headache response (no worse than mild pain at two hours) in treating acute migraine is similar to that found for some triptans (Moore 2013a).

How the intervention might work

Clinicians prescribe nonsteroidal anti-inflammatory drugs (NSAIDs) on a routine basis for mild-to-moderate pain in a range of conditions. NSAIDs are the most commonly prescribed analgesic medications worldwide, and their efficacy for treating acute pain has been well demonstrated (Moore 2011). They reversibly inhibit the activity of cyclooxygenase (prostaglandin endoperoxide synthase) (COX), now recognised to consist of two isoforms (COX-1 and COX-2), the enzyme mediating production of prostaglandins and thromboxane A2 (FitzGerald 2001).

Prostaglandins mediate a variety of physiological functions such as maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone. They also play an important role in inflammatory and nociceptive processes. However, relatively little is known about the mechanism of action of this class of compounds aside from their ability to inhibit cyclooxygenase-dependent prostanoid formation (Hawkey 1999). Fast-acting ibuprofen and diclofenac formulations used for a short time (five days) result in fewer people with erosive gastro-duodenal lesions than aspirin (Hawkey 2011). In single-dose studies in acute postoperative pain and migraine, adverse events are no more common with ibuprofen than with placebo (Derry 2009; Rabbie 2013).

Ibuprofen inhibits both COX isoforms, and suppression of prostaglandin synthesis is believed to underlie the analgesic effects of ibuprofen.

Why it is important to do this review

Episodic TTH is ubiquitous, affecting a large proportion of adults. Despite being generally mild to moderate in intensity, headache results in considerable suffering to the affected individual and contributes overall to a significant loss of productivity to society (Mannix 2001; Rasmussen 2001; Steiner 2004; Stovner 2007). Seeking relief, people generally self-medicate with one or more medicines, and OTC medicines are often used (Forward 1998). Ibuprofen is a readily accessible OTC analgesic. As a generic drug, ibuprofen could be the drug of choice or the first-line drug for management of TTH, particularly in low-resource settings. It has been shown to work in individual studies (Schachtel 1996).

Two recently published guidelines on the management of TTH have reviewed the effectiveness of treatment modalities. Both adopted a consensus methodology. The BASH guidelines are based on a limited review of studies (BASH 2010). The EFNS guidelines are based on a more detailed and thorough search of the literature (Bendtsen 2010). Moreover, the EFNS guidelines represent an improvement over the BASH guidelines in that they used a standard published protocol for developing management guidelines (Brainin 2004). That protocol strongly recommends active and frequent consultation of *The Cochrane Library*. However, there are no published Cochrane reviews on the management of acute episodic TTH. A non-Cochrane systematic review by Verhagen and others followed methods similar to those used in Cochrane reviews and evaluated the efficacy and tolerability of analgesics for treatment of acute episodes of TTH in adults, but it analysed the non-standard measure "pain relief or recovery over 2 to 6 hours" as the main efficacy outcome (Verhagen 2006).

Reviews explicitly adopting Cochrane methods and evaluating the more focused outcomes recommended in the IHS's recently updated guidelines for controlled trials of drugs in TTH are clearly important (IHS 2010). A survey of TTH study methods and reporting demonstrates that these are seldom adhered to in clinical trials, but does report a variety of outcomes, including IHS-preferred outcomes, for aspirin, ibuprofen, ketoprofen and paracetamol (Moore 2014b).

OBJECTIVES

To assess the efficacy and safety of oral ibuprofen for treatment of acute episodic TTH in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised, placebo-controlled studies (parallel-group or cross-over) using ibuprofen for symptomatic relief of an

acute episode of tension-type headache (TTH). Studies had to be prospective and include at least 10 participants per treatment arm. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately. Trials were included regardless of publication status or language of publication. We included studies conducted in any setting (home, clinic, physician's office, community centre etc.) as long as it was clear that treatment was for an acute episode of TTH.

Cross-over studies are well suited to acute episodic TTH and eliminate within-person variation. They pose challenges related to dropouts, inadequate reporting (reporting only the first period) and inappropriate reporting (reporting as parallel-group trials instead of paired observations). We included cross-over trials only if there was adequate washout (48 hours or more) between treatments and after ascertaining that the participants were adequately randomised to the first treatment period.

We excluded trials using alternation, date of birth, hospital record number or other 'quasi-random' methods of allocation of treatment.

Types of participants

Study participants were adults (18 years of age or older) with episodic TTH. We excluded studies involving participants with chronic TTH.

The diagnosis of episodic TTH had to conform to International Headache Society (IHS) criteria (IHS 2013). Other definitions were considered if they conformed in general to IHS diagnostic criteria and reasonably distinguished TTH from other headache types by specifying distinctive features of TTH; for example, absence of nausea and vomiting, mild to moderate head pain, character and location of pain, absence of obvious photophobia or phonophobia and aura, and differentiated from chronic daily headache.

We analysed data only for people with acute TTH episodes. We had planned to separately analyse infrequent and frequent episodic TTH, but all included studies enrolled participants with frequent episodic TTH (IHS 2013). Studies including participants with 'mixed' migraine and TTH, or 'combination' headaches, would have posed problems as these terms may have referred to patients with discrete episodes of migraine and discrete episodes of TTH, or to patients with headaches which (in the view of the investigators) combined features of migraine and TTH. The IHS criteria assign a dual diagnosis of migraine and TTH or 'probable migraine', respectively, to such patients. In such situations we expected that the headache pattern denoted by these terms would be described, and planned to consider on a case-by-case basis their inclusion or exclusion from the review. However, no such problems arose. Secondary headache disorders were excluded using criteria based on International Classification of Headache Disorders (ICHD) criteria (IHS 2013).

Types of interventions

Included studies had to have at least one arm in which ibuprofen was given orally for the treatment of an acute episode of TTH. There was no restriction on dose. Included studies could use either a single dose to treat a discrete headache episode or investigate different dosing strategies.

A placebo comparator is essential to demonstrate that ibuprofen is effective in this condition. The placebo used had to be identical to ibuprofen in appearance (size, colour etc.) and the number of tablets. Active-controlled trials without a placebo were considered as secondary evidence.

Types of outcome measures

Primary and secondary outcomes selected for analysis reflected the updated guidelines for controlled trials of drugs in TTH issued by the IHS (IHS 2010).

Primary outcomes

The primary outcome was the pain-free rate at the end of two hours using any standard method of pain assessment and without the use of rescue medication.

Secondary outcomes

1. Pain-free rate at different time points, without the use of rescue medication. We considered 1 hour, 4 hours, and 24 hours as clinically important endpoints and planned to analyse them separately.
2. Pain Intensity Difference (PID) and Sum of Pain Intensity Difference (SPID), without the use of rescue medication, were separately analysed.
3. No worse than mild pain at two hours (equivalent to headache response in migraine trials); this is an outcome regarded as useful by most people with acute or chronic pain (Moore 2013b).
4. Adverse events: number of participants with any adverse event, identity and rates of specific adverse events (where available), number of participants with serious adverse events, number of withdrawals due to adverse events, and all cause withdrawals.
5. Use of rescue medication.

Search methods for identification of studies

Electronic searches

We searched the following databases.

1. Cochrane Central Register of Controlled Trials (CENTRAL) Issue 12 of 12, 2014 (via *The Cochrane Library*);
2. MEDLINE (via PubMed) (1966 to 15 January 2015);
3. EMBASE (via Ovid) (1966 to 15 January 2015);
4. Oxford Pain Relief Database (Jadad 1996a).

The search strategies for CENTRAL, MEDLINE, and EMBASE are reported in Appendix 1, Appendix 2, and Appendix 3.

Searching other resources

On January 15 2015 we searched the WHO International Clinical Trials Registry Platform (ICTRP 2010) and ClinicalTrials.gov for completed or ongoing trials using the key words 'headache' or 'cephalalgia' or their variations (using wildcards).

We also searched the reference lists of all eligible studies and previous systematic reviews for additional studies.

We examined web-based clinical trial registries of manufacturers of ibuprofen including GlaxoSmithKline, Novartis, Bayer, and Reckitt Benckiser to attempt to identify unpublished studies.

Data collection and analysis

Selection of studies

Two authors independently reviewed the titles and abstracts of all studies identified through searching to exclude any that clearly did not satisfy the inclusion criteria, and read full copies of the remaining studies to identify those suitable for inclusion. We resolved disagreements by discussion, or by referral to a third author for independent review and a final decision.

Data extraction and management

We adapted the Cochrane Pain, Palliative and Supportive Care Review Group's data extraction form to suit the requirements of the present review. Two authors independently extracted data from each study using the form. Disagreements and uncertainties were resolved by discussion. One author entered data into Review Manager 5.3 (RevMan 2014).

Assessment of risk of bias in included studies

We used the Oxford Quality Score as the basis for inclusion, limiting inclusion to studies that were randomised and double-blind as a minimum (Jadad 1996b). The scores for each study are reported in the 'Characteristics of included studies' table.

Two authors independently assessed the risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and adapted from those used by the Cochrane Pregnancy and Childbirth Group, and resolved any disagreements by discussion. We assessed the following for each study.

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process such as random number table or computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (for example, odd or even date of birth; hospital or clinic record number).
2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (for example, telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation and were therefore at high risk of bias (for example, open list).
3. Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding; for example, identical tablets, matched in appearance and smell); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved). We excluded studies that were not double-blind.
4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (less than 10% of participants did not complete the study or the study used 'baseline observation carried forward' analysis, or both); unclear risk of bias (used 'last observation carried forward' analysis); high risk of bias (used 'completer' analysis).
5. Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (fewer than 50 participants per treatment arm).

Measures of treatment effect

We used risk ratio (RR) to establish the statistical difference, and the numbers needed to treat (NNT) and pooled percentages as absolute measures of benefit or harm.

We used the following to describe adverse outcomes in terms of harm or prevention of harm.

- When significantly fewer adverse outcomes occurred with ibuprofen than with control (placebo or active) we used the term the number needed to treat to prevent one event (NNTp).
- When significantly more adverse outcomes occurred with ibuprofen compared with control (placebo or active) we used the term the number needed to treat to harm or cause one event (NNH).

When continuous outcomes were reported we used them in analyses where possible. We have reported 95% confidence intervals (CIs) for all measures.

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

The most likely source of missing data was expected to be cross-over studies; we planned to use only first-period data where possible, but where that was not provided we planned to treat the results as if they were parallel-group results. We have commented where there were substantial missing data in any study.

For all outcomes we carried out analyses, as far as possible, on a modified intention-to-treat basis; that is, we included all participants who were randomised and received an intervention. Where sufficient information was reported, we have re-included missing data in the analyses undertaken. We planned to exclude data from outcomes where results from 10% or more of participants were missing with no acceptable reason provided or apparent.

Assessment of heterogeneity

We assessed heterogeneity of response rates using L'Abbé plots, a visual method for assessing differences in results of individual studies (L'Abbé 1987). Where data were pooled, we have reported the I^2 statistic.

Assessment of reporting biases

We planned to assess the risk of publication bias by examining the number of participants in trials with zero effect (relative risk of 1.0) needed for the point estimate of the NNT to increase beyond a clinically useful level (Moore 2008). In this case, we specified a

clinically useful level as an NNT of 10 or more for 'pain free at two hours', and NNT of 8 or more for 'no worse than mild pain at two hours'.

Data synthesis

All studies used a single dose of ibuprofen in established pain of at least moderate intensity. No included studies treated mild headaches or investigated treatment with a second dose of medication.

We analysed separately the different doses of ibuprofen. There were insufficient data to analyse separately infrequent and frequent episodic TTH.

We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants (Moore 1998). We calculated RR for benefit or harm with 95% CIs using a fixed-effect model (Morris 1995), and calculated NNT, NNTp and NNH with 95% CIs using the pooled number of events by the method of Cook and Sackett (Cook 1995). A statistically significant difference from control was assumed when the 95% CI of the relative risk of benefit or harm did not include the number one.

We planned to use the z test to determine significant differences between NNT, NNTp and NNH for different groups in subgroup and sensitivity analyses (Tramèr 1997).

We have described data from comparisons and outcomes with only one study or fewer than 200 participants in the text and summary tables where appropriate for information and comparison, but have not analysed them quantitatively.

Subgroup analysis and investigation of heterogeneity

We planned to carry out subgroup analysis for formulation, with separate analyses for standard ibuprofen acid and for fast-acting formulations (Moore 2014a; Moore 2015). A minimum of two studies and 200 participants had to be available for any subgroup analysis.

Sensitivity analysis

We planned a sensitivity analysis for study quality (Oxford Quality Score of 2 versus 3 or more), but no study scored less than 3/5.

RESULTS

Description of studies

Results of the search

Searches identified 173 potential studies in CENTRAL, 220 in MEDLINE, and 816 in EMBASE. Fifteen studies were read in full: eight from literature searches, five identified in Clinicaltrials.gov, and two clinical study reports provided by Reckitt Benckiser (Figure 1).

Figure 1. Study flow diagram. CSR = clinical study report

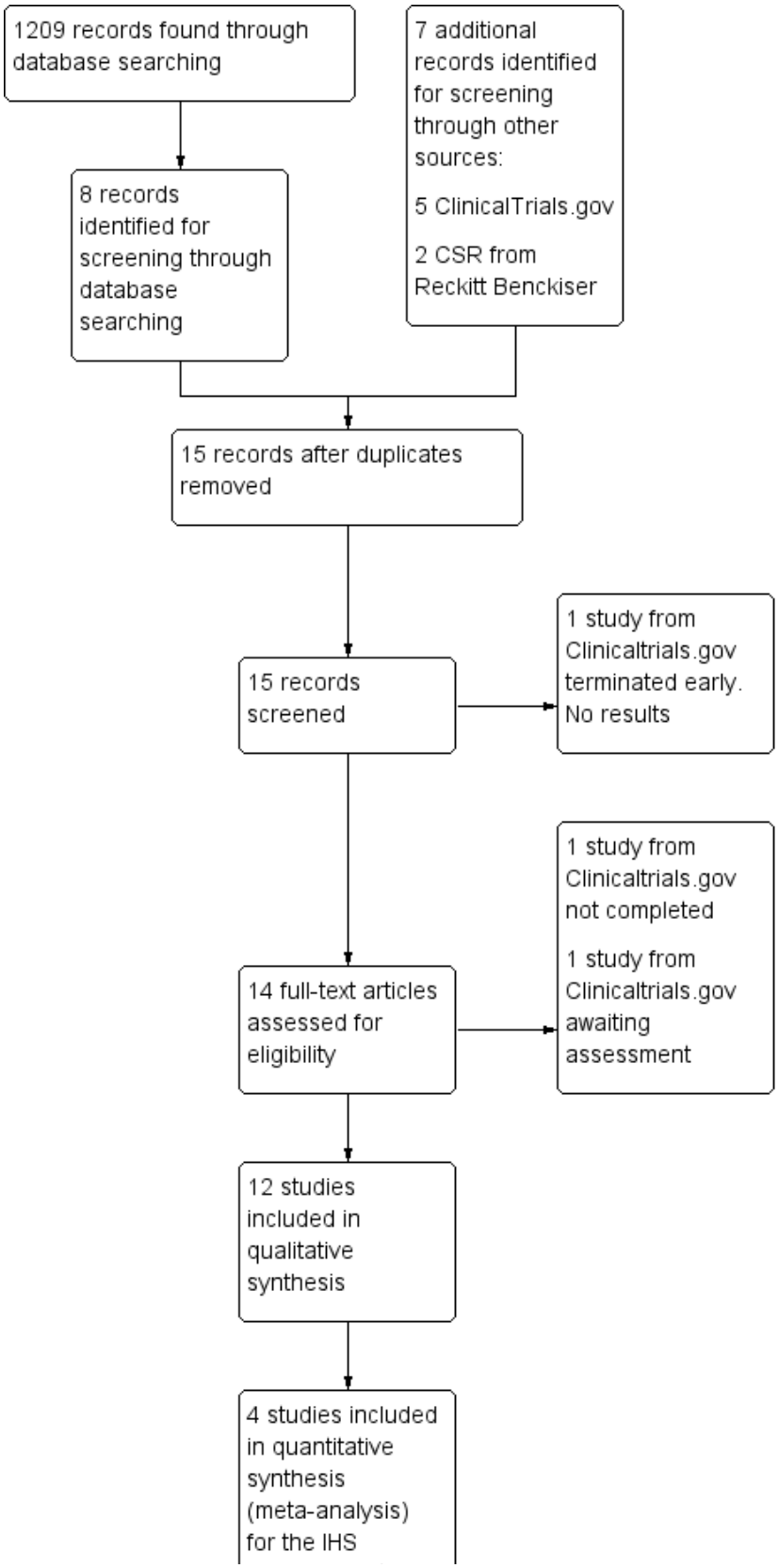
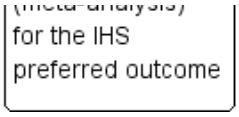


Figure 1. (Continued)



We excluded one because it was terminated before being completed, and had no results. Of the 14 included studies, one study was completed in April 2004, but no study results are available (NCT01464983). We have placed this study in the 'Studies awaiting assessment' category while further information is sought. Another study was due to complete in March 2015 and we have placed this in 'Ongoing studies' (NCT01842633).

Included studies

We included 12 studies (3094 participants), all of which enrolled adult participants with frequent episodic TTH (Diamond 2000; Kubitzek 2003; Lange 1995; Laveneziana 1996; NCT01077973; NCT01362491; NL9701; NU2104; Packman 2000; Schachtel 1988; Schachtel 1996; van Gerven 1996). Nine used the IHS diagnostic criteria, but two used the older classification of the Ad Hoc Committee (Ad Hoc Committee 1962; Schachtel 1988; Schachtel 1996), and one did not describe diagnostic criteria (NU2104). We included this last study because it clearly excluded participants with migraines; we planned to carry out a subgroup analysis excluding it from efficacy analyses, but it did not contribute to these analyses.

Studies typically did not report the average headache frequency in participants. NL9701 reported that the average headache frequency was 6 per month. Lange 1995 reported that 13% of participants had chronic TTH, but this study contributed no data for analysis as it had no placebo control and tested only a 200 mg ibuprofen dose.

Two studies used a cross-over design (Laveneziana 1996; NU2104) and the remainder used parallel groups. In all cases a single dose of study medication was used to treat a discrete headache episode of at least moderate intensity. Neither of the cross-over studies reported data for the first period alone. One specified at least 48 hours between successive attacks (NU2104). The other did not specify any period without treatment, although treatment with any analgesic within 12 hours was an exclusion criterion (Laveneziana 1996).

Participants had moderate or severe pain at the start of treatment. Outcomes were not consistently reported in the studies. Pain free at 2 hours was reported in six studies, pain free at 1 hour in four, a global evaluation of very good or excellent in five, and pain intensity difference in four. No study reported the numbers with no worse than mild pain at one or two hours. Adverse event numbers were reported in six studies, with four reporting no adverse events. Rescue medication use was reported in four studies.

Two studies used ibuprofen 200 mg (Lange 1995; van Gerven 1996). One compared S+ ibuprofen 200 mg with racaemic ibuprofen 400 mg (NU2104). Another used the arginine salt of ibuprofen but did not provide the dose(Laveneziana 1996).

The remaining studies used ibuprofen 400 mg, either as the standard acid formulation (Diamond 2000; Kubitzek 2003; Lange 1995; NCT01077973; NCT01362491; NL9701; Schachtel 1988; Schachtel 1996; van Gerven 1996), the sodium salt (NCT01077973; NCT01362491), or a liquigel (Packman 2000). These salts and the liquigel formulation are believed to be more soluble than the standard acid formulation and to enter the circulatory system more rapidly. NCT01077973 and NCT01362491 directly compared the sodium salt with the standard formulation and placebo. All studies included a placebo control except Lange 1995 and NU2104.

Active comparators were:

- ibuprofen 400 mg + caffeine 200 mg and caffeine 200 mg alone (Diamond 2000);
- potassium diclofenac 12.5 mg and 25 mg (Kubitzek 2003);
- ketoprofen 12.5 mg and 25 mg (Lange 1995; van Gerven 1996);
- naproxen 275 mg (Lange 1995);
- paracetamol 1000 mg (NL9701; Packman 2000; Schachtel 1996); and
- piroxicam beta-cyclodextrin (Laveneziana 1996).

The total number of participants in the 12 studies was 3094, with 3000 in parallel-group studies and 94 in crossover studies. Placebo was taken by 733 participants, ibuprofen standard formulation 200 mg by 127, ibuprofen standard formulation 400 mg by 892, ibuprofen fast-acting formulation 400 mg by 230, ibuprofen combined with another drug by 97, other NSAID by 651, and any other analgesic (mainly paracetamol) by 458.

The number of participants with data for analyses for ibuprofen was therefore much smaller than the total number. Because outcomes were inconsistently reported (Appendix 4), the number of participants in important analyses of efficacy was even smaller than this.

Excluded studies

We excluded one study because it had been terminated early due to poor recruitment and there were no study results available (NCT01755702). The study was designed to compare ibuprofen, paracetamol, paracetamol plus caffeine, and placebo. The report did not provide doses of the interventions.

Risk of bias in included studies

Risk of bias is shown in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

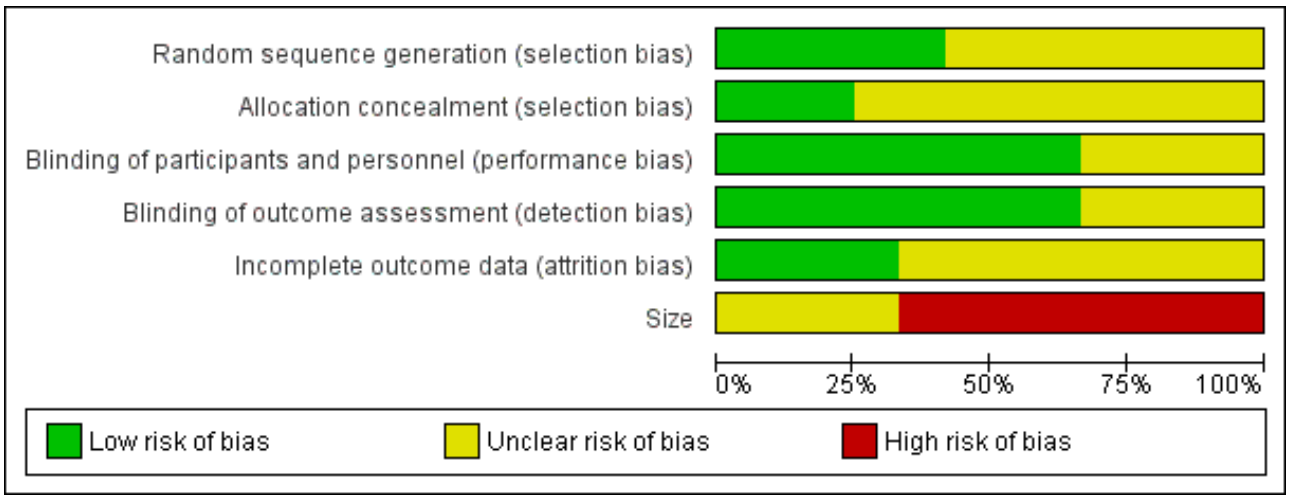
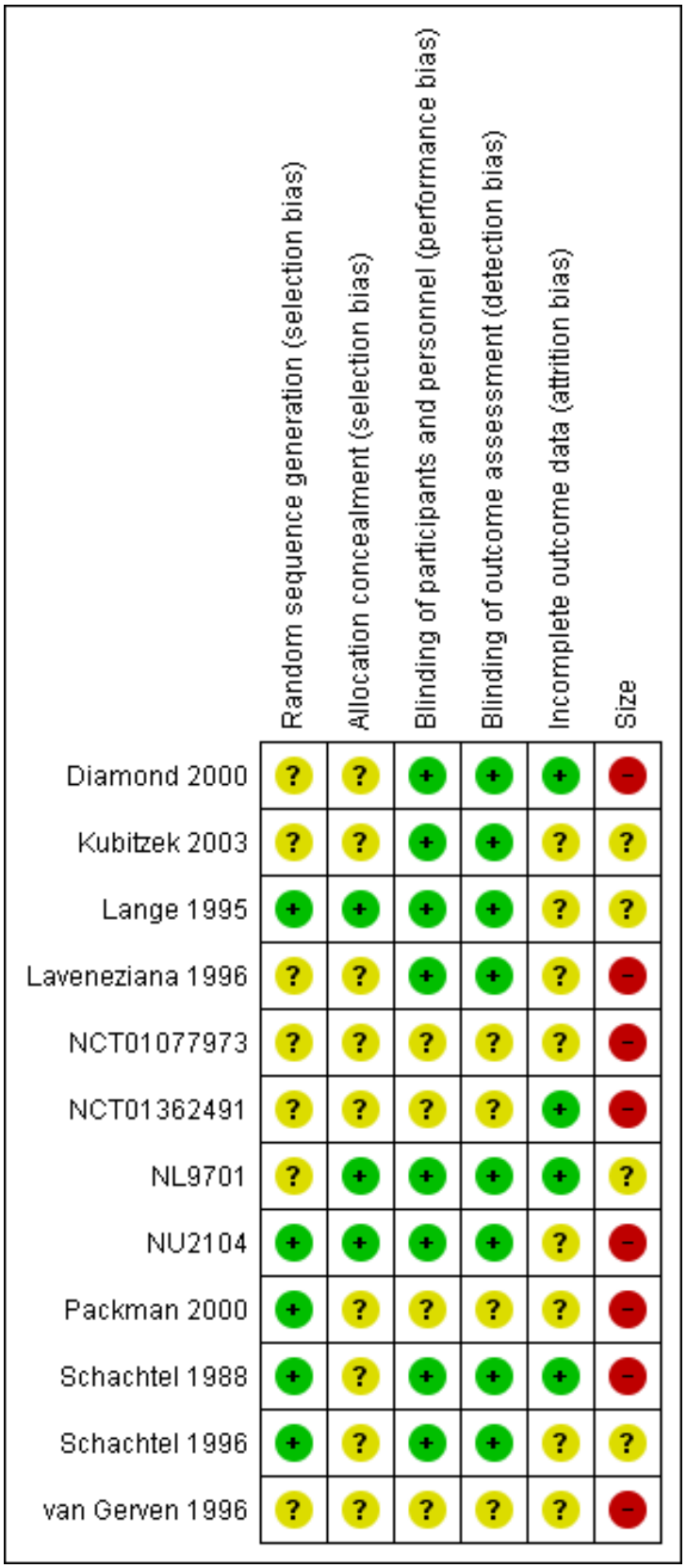


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All studies were randomised, but only five adequately described the methods used to generate the random sequence (Lange 1995; NU2104; Packman 2000; Schachtel 1988; Schachtel 1996). Three studies adequately described the method used to conceal the random allocation (Lange 1995; NL9701; NU2104).

Blinding

All studies were double blind, and eight adequately described the methods used to conceal the intervention from participants and personnel (Diamond 2000; Kubitzek 2003; Lange 1995; Laveneziana 1996; NL9701; NU2104; Schachtel 1988; Schachtel 1996).

Incomplete outcome data

Three studies convincingly accounted for all participants in the primary outcome (Diamond 2000; NCT01362491; NL9701). We judged the remaining studies to be at unknown risk of bias due to a lack of information.

Other potential sources of bias

No studies enrolled 200 or more participants per treatment arm (low risk of bias), while three enrolled between 50 and 199 (unknown risk of bias) (Kubitzek 2003; Lange 1995; NL9701). The remaining studies all included at least one treatment arm with fewer than 50 participants, which we judged to be at high risk of bias.

Effects of interventions

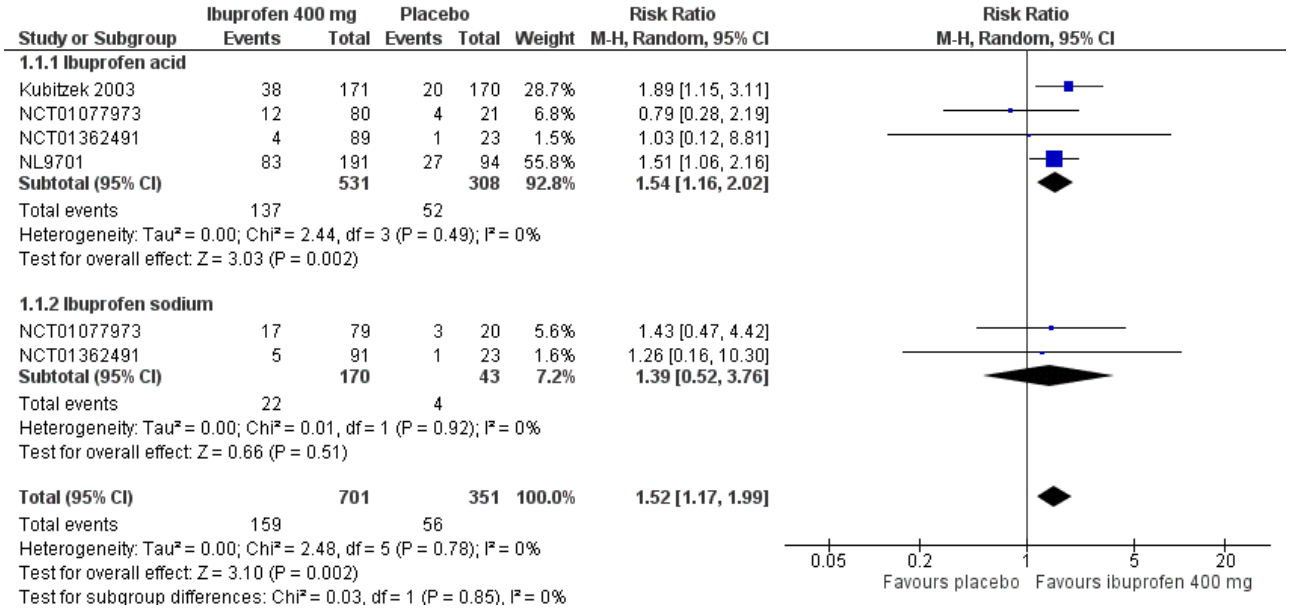
See: **Summary of findings for the main comparison**

Ibuprofen 400 mg versus placebo

Pain-free at two hours

Four studies contributed data for this analysis. All the studies included a treatment arm using a standard formulation, but two also had treatment arms that used the sodium salt at an equivalent dose (NCT01077973; NCT01362491). There were no obvious differences between the two formulations for this outcome, and limited amounts of data, so we have combined the results for standard and sodium formulations in each study for this analysis. Analysis 1.1 and Figure 4 show the results by ibuprofen formulation.

Figure 4. Forest plot of comparison: 1 ibuprofen 400 mg versus placebo, outcome: 1.1 Pain-free at 2 hours.



- The proportion of participants who were pain-free at two hours with ibuprofen was 23% (159/701, range 5% to 43%).
- The proportion of participants who were pain-free at two hours with placebo was 16% (56/351, range 2% to 29%).
- The relative benefit of treatment compared with placebo was 1.5 (95% CI 1.2 to 2.0); the NNT was 14 (8.4 to 47) (Analysis 1.1).

Pain-free at one hour

Three studies contributed data for this analysis (NCT01077973; NCT01362491; NL9701). We have combined results for standard and sodium formulations in each study for this analysis.

- The proportion of participants who were pain-free at one hour with ibuprofen was 6.3% (33/530, range 0% to 14%).
- The proportion of participants who were pain-free at one hour with placebo was 5.8% (10/181, range 1% to 10%).
- The relative benefit of treatment compared with placebo was 1.5 (0.8 to 2.9). NNT was not calculated (Analysis 1.2).

Pain intensity difference at two hours

Few studies reported this outcome, and those that did used different scales, so no analysis was possible.

Patient global evaluation of treatment

Three studies (739 participants) contributed data for this analysis (Diamond 2000; Kubitzek 2003; NL9701). All used a standard formulation of ibuprofen.

- The proportion of participants reporting a global evaluation equivalent to 'very good' or 'excellent' with ibuprofen was 40% (176/443, range 24% to 51%).
- The proportion of participants reporting a global evaluation equivalent to 'very good' or 'excellent' with placebo was 23% (67/296, range 17% to 35%).
- The relative benefit of treatment compared with placebo was 1.7 (1.3 to 2.1); the NNT was 5.9 (4.2 to 9.5) (Analysis 1.3).

No worse than mild pain at two hours

No studies reported this outcome.

Adverse events

Any adverse event

Eight studies (1645 participants) contributed data for this analysis (Diamond 2000; Kubitzek 2003; NCT01077973; NCT01362491; NL9701; Packman 2000; Schachtel 1988; Schachtel 1996).

- The proportion of participants who experienced any adverse event with ibuprofen was 4.1% (42/1035, range 0% to 12%).
- The proportion of participants who experienced any adverse event with placebo was 3.8% (23/610, range 0% to 13%).
- The relative benefit of treatment compared with placebo was 1.1 (0.6 to 1.7); the NNH was not calculated (Analysis 1.4).

Serious adverse events

There were no serious adverse events in any of the studies.

Withdrawals

There were no withdrawals due to adverse events in any of the studies.

Ibuprofen 200 mg versus placebo

Only one study compared ibuprofen 200 mg with placebo (van Gerven 1996). It did not provide any usable efficacy data, while 3/40 participants experienced an adverse event with ibuprofen 200 mg and 2/39 with placebo.

Ibuprofen versus active comparators

Only single studies provided data comparing ibuprofen 400 mg or 200 mg with diclofenac potassium 12.5 mg and 25 mg (Kubitzek 2003), naproxen 275 mg (Lange 1995), and piroxicam (Laveneziana 1996); two studies provided data comparing ibuprofen 400 mg or 200 mg with ketoprofen 12.5 mg and 25 mg (Lange 1995; van Gerven 1996); and three studies provided data comparing ibuprofen 400 mg or 200 mg with paracetamol (NL9701; Packman 2000; Schachtel 1996). Results for individual studies are in Appendix 4 and Appendix 5.

Use of rescue medication

Six studies did not provide any data for use of rescue medication (Diamond 2000; Lange 1995; NU2104; Packman 2000; Schachtel 1988; Schachtel 1996). Two studies reported that no participants used any rescue medication (NCT01077973; NCT01362491), one study reported the specific time at which participants took additional medication (Laveneziana 1996), and one reported numbers taking additional medication at the earliest opportunity (2 hours) (van Gerven 1996).

The remaining two studies investigating the use of ibuprofen 400 mg reported the use of rescue medication over 6 hours (Kubitzek 2003; NL9701).

- The proportion of participants who used rescue medication over 6 hours with ibuprofen was 15% (50/342, range 13% to 17%).
- The proportion of participants who used rescue medication over 6 hours with placebo was 26% (64/247, range 20% to 29%).
- The relative risk of treatment compared with placebo was 0.59 (0.42 to 0.83); the NNTp was 8.9 (5.6 to 21) (Analysis 1.5).

DISCUSSION

Summary of main results

This review is characterised by limited amounts of information for the use of ibuprofen to treat acute tension-type headache, the commonest cause of acute pain (Vos 2012). Participants had moderate or severe pain at the start of treatment, and for the outcome preferred by the International Headache Society (IHS) of being pain free at 2 hours the NNT for ibuprofen 400 mg compared with placebo was 14 (8.4 to 47), with no significant difference from placebo at 1 hour. A better NNT of 5.9 (4.2 to 9.5) was recorded for a global evaluation of 'very good' or 'excellent'. There was insufficient or no data for outcomes of participants experiencing no worse than mild pain at 1 or 2 hours, arguably outcomes of interest to people with acute tension headache, as it is across all types of pain (Moore 2013b). The use of rescue medication was lower with ibuprofen 400 mg than with placebo, with a NNTp of 8.9 (5.6 to 21).

Although some studies examined ibuprofen acid formulation, and some fast-acting ibuprofen formulations, results were inconsistent. Nor was there any information for doses other than 400 mg. It might be argued that results from acute postoperative pain suggest that both fast acting formulations and higher doses of ibuprofen would deliver greater efficacy (Derry 2009; Moore 2011; Moore 2014a; Moore 2015). Other analgesic drugs have similar limited efficacy in acute tension headache, but the amount of information available on analgesic efficacy is very limited (Moore 2014b).

A single 400 mg dose of ibuprofen produced the same rate of adverse event reporting as did placebo, in an analysis based on substantially more participants (1645) than for any single efficacy calculation. This accords with results of single dose use in postoperative pain (Bendtsen 2010; Moore 2011).

Overall completeness and applicability of evidence

The information from clinical trials is inadequate in terms of doses and formulations studied, and outcomes reported. Given the known limited efficacy from 400 mg doses, it might have been expedient to explore a higher dose. A 400 mg dose of ibuprofen represents only one-sixth of the recommended daily dose of 2,400 mg, and, for example, 600 mg single doses are used in some parts of the world. An argument against higher doses might be the lack of a strong dose-response of ibuprofen in acute postoperative pain, though doses of 200 mg and above are highly

effective in that circumstance (Derry 2009). Again in acute pain, fast-acting formulations have proven to be much more effective than standards ibuprofen acid (Moore 2014a; Moore 2015). In this review of ibuprofen in TTH, studies using fast-acting ibuprofen had low success rates for all interventions, and that might suggest some form of model failure (Figure 4).

IHS recommendations regarding outcomes of headache trials are well regarded, and often, if not always, followed (Bendtsen 2010; Moore 2014b). Trials included in this review were inconsistent in reporting outcomes recommended by the IHS, and this limited the ability to draw useful conclusions about the efficacy of ibuprofen. No trial reported on participants with no worse than mild pain at one or two hours. Ketoprofen 25 mg, but not paracetamol 1000 mg, has substantially lower (better) NNTs for this outcome than pain free at 2 hours (Moore 2014b). It is possible that the current IHS-preferred outcome is too stringent as a measure of treatment success if a range of interventions fail to produce reasonable levels of efficacy for this outcome.

The results are difficult to extrapolate to people who have an occasional headache.

Quality of the evidence

All included studies were both randomised and double-blind; none were considered at high risk of methodological bias. Inconsistent reporting of outcomes, and the small size of a number of the studies were the major problems with the available studies.

None of the included studies provided information on the average number of headaches experienced by participants before study entry, although all studies required participants to have frequent episodic TTH. This is defined as anywhere between 2 and 15 headache days a month. We do not know whether the participants in these studies were typically experiencing 2 to 5, or more than 10 headaches a month. This might influence the efficacy of treatments tested in these TTH studies, but we do not know because the information is missing.

What is required to try to understand these important methodological points is analysis of clinical trials at the level of the individual patient, using substantial amounts of data. Currently that looks unlikely, but such an analysis would probably be highly informative for the development of existing IHS guidance (Bendtsen 2010).

Potential biases in the review process

We know of no potential biases in the review process. We know of no relevant unpublished studies. The potential effects of unpublished data with no treatment effect is irrelevant given the limited efficacy from the results of this review.

Agreements and disagreements with other studies or reviews

These results are broadly in agreement with previous reviews that concluded that ibuprofen, paracetamol, and ketoprofen were better than placebo (Moore 2014b; Verhagen 2006), as well as the guideline from the European Federation of Neurological Societies which recommends ibuprofen as drug of choice among NSAIDs or paracetamol or aspirin for acute treatment of TTH (Bendtsen 2010). That guideline was not based on a systematic review. The German evidence-based recommendations for self-medication of migraine and TTH were based on systematic reviews (Haag 2011), and included only seven studies that included at least some people with TTH. For self-medication of TTH it recommended ibuprofen along with a number of other medicines, some of which are not supported by any significant data.

AUTHORS' CONCLUSIONS

Implications for practice

For people with episodic tension-type headache

Ibuprofen 400 mg may relieve headache pain, but the chance of the pain being relieved entirely by 2 hours is low. We do not know how or if these results can be extrapolated to people with an occasional headache.

For clinicians

While ibuprofen 400 mg is one choice for treatment of episodic TTH, it may be that higher doses or different formulations might be better, but evidence on this is lacking. Ibuprofen 400 mg is probably not much different from any other treatment, based on what is known.

For policy makers

There is insufficient information on drugs, doses, formulations, or outcomes to be able to make strong recommendations.

For funders

There is insufficient information on drugs, doses, formulations, or outcomes to be able to make confident decisions on cost effectiveness.

Implications for research

General

Episodic TTH is common and debilitating. The amount and reporting of evidence was limited by reporting issues, particularly of outcomes; this is a general finding for all TTH studies, not just those involving ibuprofen. It is not sufficient just to call for more studies. What is needed is a better understanding of TTH studies, in terms of the outcomes that can be reported from clinical trials, and often is not, and the differential effects of treatments in people with different degrees of headache frequency. This can be done from individual participant-level analyses. Given that a number of modern studies have been completed or are underway, this would appear to be the research priority before new studies are commissioned.

Design

The design of studies was generally good, though some were small.

Measurement (endpoints)

The measurement of pain is not a major issue, as most studies, especially modern studies, have used standard pain intensity and pain relief scales. What is at issue are the outcomes reported using those pain measurements. It is not clear that the IHS-preferred outcome of being free of pain at 2 hours is entirely appropriate, and while it is reasonable by analogy with migraine, it requires substantiating.

Comparison between active treatments

No authoritative comparisons between active treatments is possible in the present state of knowledge.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Diamond 2000

Methods	Randomised, double-blind, parallel groups, placebo- and active-controlled, single-dose study Multicentre Assessment at 0, 15, 30, 45, 60, 90, 120 minutes, then hourly to 6 h
Participants	Episodic TTH (IHS criteria), 3 to 15 episodes per month in previous year, responsive ≥ 75% of the time to nonprescription-strength analgesics. Able to distinguish TTH from migraine (migraine < 3 attacks per month not excluded). Age ≥ 18 years N = 331 (301 eligible for analysis) Mean age 37 years (range 18 to 73) M 57, F 244 92% White Usual frequency of headaches not reported Baseline PI ≥ moderate (24% severe at dosing)

Diamond 2000 *(Continued)*

Interventions	Ibuprofen 400 mg + caffeine 200 mg, n = 97 Ibuprofen 400 mg, n = 99 Caffeine 200 mg, n = 57 Placebo n = 48 Rescue medication allowed after two hours
Outcomes	PI: none, slight, moderate, severe (0 to 3) PR: none, a little, some, a lot, complete (0 to 4) SPID and TOTPAR at 4 and 6 h calculated Onset and meaningful analgesia PGE: poor, fair, good, very good, excellent (0 to 4) AEs
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Study medications were supplied as identical tablets"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Study medications were supplied as identical tablets"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Excluded participants accounted for
Size	High risk	< 50 participants per treatment arm (≤ 30)

Kubitzek 2003

Methods	Randomised, double-blind (double-dummy), parallel groups, placebo- and active-controlled, single-dose study Multicentre Assessment at 0, 30, 60 minutes, then hourly to 6 h
Participants	Episodic TTH (IHS criteria), < 15 episodes per month and < 180 episodes per year, previous episodes lasting 30 minutes to 7 days, regularly used OTC medication for TTH, onset before age 50. Adult N = 684 randomised, 620 treated a headache Mean age 42 years 44% male

Kubitzek 2003 *(Continued)*

	98% Caucasian Frequency 3 to 6 per month 60% Frequency > 6 per month 17% Baseline PI ≥ moderate (45% severe)
Interventions	Ibuprofen 400 mg, n = 151 Diclofenac-K 12.5 mg, n = 160 Diclofenac-K 25 mg, n = 156 Placebo, n = 153 Medication taken ≥ 30 minutes after onset of pain, when PI ≥ moderate Rescue medication (paracetamol 500 mg) allowed after two hours
Outcomes	PI: none, mild, moderate, severe (0 to 3) PR: none, a little, some, a lot, complete (0 to 4) SPID and TOTPAR at 3 and 6 h calculated PGE: poor, fair, good, very good, excellent (0 to 4) Use of rescue medication AEs
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-dummy design was used"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"double-dummy design was used"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of imputation. ≤ 2% withdrawals not specified
Size	Unclear risk	50 to 200 participants per treatment arm (170 to 172)

Lange 1995

Methods	Randomised, double-blind, parallel groups, active-controlled, single-dose study Multicentre

Lange 1995 *(Continued)*

	Assessment at 0, 30, 45, 60 minutes, then hourly to 4 h
Participants	TTH (IHS criteria). Age 18 to 65 years. Participants with other types of headache were excluded N = 345 Mean age 43 years (range 18 to 66) M 110, F 235 Ethnic origin not reported Usual frequency of headaches not reported Baseline pain ≥ moderate (mean 3.7 ± 0.6, scale 1 to 4)
Interventions	Ibuprofen 200 mg, n = 87 Ketoprofen 12.5 mg, n = 86 Ketoprofen 25 mg, n = 87 Naproxen 275 mg, n = 85 Medication taken with an adequate amount of water when PI ≥ moderate 13% had a diagnosis of chronic TTH Rescue medication allowed after two hours
Outcomes	PI: none, mild, moderate, severe (1 to 4) PR: none, poor, moderate, good, complete (i to v) SPID at 4 h calculated Pain-free at 4 h PGE: poor, fair, good, very good, excellent (0 to 4) AEs
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomised by computer"
Allocation concealment (selection bias)	Low risk	Medicines identified only by random number and allocated in ascending order
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"enclosing the single doses in neutral packaging"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"enclosing the single doses in neutral packaging"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of withdrawals or imputation method
Size	Unclear risk	50 to 200 participants per treatment arm (85 to 87)

Laveneziana 1996

Methods	Randomised, double-blind (double dummy), active-controlled, cross-over study. Single dose of each medication Single centre Assessment at 0, 15, 30, 60 minutes and at 2, 4 h
Participants	Episodic TTH (IHS criteria), 2 to 5 episodes per month, requiring treatment and responsive to aspirin or NSAIDs. Participants with mild or very severe headaches were excluded. Age ≥ 18 years N = 30 (26 analysed for efficacy) No demographic data provided Baseline PI approximately 60/100
Interventions	Ibuprofen Argenine Beta-cyclodextrin piroxicam Placebo Drug doses not given Rescue medication allowed after one hour
Outcomes	PI: 100 mm VAS over 4 h PGE: 5-point categorical scale over 4 h Rescue medication Adverse events
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double dummy method
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double dummy method
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of imputation. Exclusions approximately 10%
Size	High risk	< 50 participants per treatment arm (≤ 30)

NCT01077973

Methods	Randomised, double-blind, parallel groups, active-controlled, single-dose study Assessment over 3 h
Participants	Episodic TTH (IHS criteria), 4 episodes per month of moderate severity for last 6 months, generally lasting > 3 h if untreated, adequate relief usually obtained with normal doses of OTC medication. Age 18 to 65 years N = 200 Mean age 42 years M 62, F 138 Ethnic origin not reported Usual frequency of headaches not reported Baseline PI ≥ moderate (27% severe)
Interventions	Ibuprofen sodium 400 mg, n = 79 Ibuprofen standard 400 mg, n = 80 Placebo, n = 41 Rescue medication allowed, but was not used by any participant
Outcomes	PR: no relief to complete relief (0 to 4) PI: none to severe (0 to 3) PID at 1, 2, 3 h calculated TOTPAR and SPRID calculated at 3 h Time to onset of meaningful relief Time to perceptible relief Participants with meaningful relief, perceptible relief Treatment failure Complete relief
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported

NCT01077973 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details reported
Size	High risk	< 50 participants in each treatment arm (41 to 80)

NCT01362491

Methods	Randomised, double-blind (double-dummy), parallel groups, placebo- and active-controlled, single-dose study Assessment over 3 h
Participants	Episodic TTH (IHS criteria). Age 18 to 65 years N = 226 Mean age 43 years M 77, F 149 Ethnic origin not reported Usual frequency of headaches not reported Baseline pain ≥ moderate (21% severe)
Interventions	Ibuprofen sodium = ibuprofen 400 mg, n = 91 Standard ibuprofen 400 mg, n = 89 Placebo, n = 46 Rescue medication probably available, but not used
Outcomes	PI: none to severe (0 to 3) PR: none to complete (0 to 4) SPID at 2 h and 3 h calculated TOTPAR at 2 h and 3 h calculated SPRID at 1, 2, and 3 h calculated Time to perceptible and meaningful relief Participants with perceptible and meaningful relief at 0.5, 1, 2, 3 h Complete relief Withdrawals Adverse events
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3/5 Email to investigators asking for additional information on methods and participants with ≤ mild pain at 1 and 2 h (20 January 2015)

Risk of bias

NCT01362491 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants in ITT analysis
Size	High risk	< 50 participants in each treatment arm (46 to 91)

NL9701

Methods	Randomised, double-blind (double-dummy), parallel groups, placebo- and active-controlled, single-dose study Assessment at 0, 15, 30, 45, 60 minutes and 2, 3, 4, 5, 6 h, and 24 h if no rescue medication taken
Participants	Episodic TTH (IHS criteria), one-year history, 2 to 10 episodes per month, ≥ moderate intensity. Age 18 to 65 years, onset before age 50. Participants experiencing > 1 migraine per month were excluded N = 513 randomised, 480 treated a headache (473 evaluable) Mean age 31 years (range 18 to 63) M 125, F 348 Ethnic origin not reported Mean headaches per month 5.7 ± 2.5, usually lasting 4 h to 5 days if untreated Baseline PI ≥ moderate (15% severe)
Interventions	Ibuprofen 400 mg, n = 191 Paracetamol 1000 mg, n = 188 Placebo, n = 94 Medication swallowed whole with 6 to 8 fluid ounces of water Rescue medication allowed after two hours
Outcomes	PI: none, mild, moderate, severe (0 to 3) PR: none, a little, some, a lot, complete (0 to 4) Pain-free at 2 h Functional impairment: none, mild, moderate, severe (0 to 3)

NL9701 *(Continued)*

	PGE: poor, fair, good, very good, excellent (0 to 4) TOTPAR and SPID at 2, 4, 6 h calculated Meaningful relief Rate of recurrence Use of rescue medication Comparison with usual medication: worse, a little worse, same, a little better, better (−2 to +2) Adverse events
Notes	Oxford Quality Score: R = 1, DB = 2, W = 1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of randomisation method not reported
Allocation concealment (selection bias)	Low risk	Medication supplied in wallets identified by randomisation ID. Allocated consecutively
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double dummy method
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double dummy method
Incomplete outcome data (attrition bias) All outcomes	Low risk	BOCF for withdrawals where there is no evidence that headache resolved, LOCF if there is evidence that headache resolved
Size	Unclear risk	50-199 participants per treatment arm (94-191)

NU2104

Methods	Randomised, double-blind (double-dummy), active-controlled, cross-over study. Single dose of each medication with minimum of 24 h between treatments Multicentre Assessments at 0, 15, 30, 60 minutes and 2, 3, 4 h
Participants	People seeking treatment from GP for frequent muscle contraction (tension) headaches of ≥ moderate severity, experienced ≥1 per month. No diagnostic criteria mentioned. Participants who experienced migraine were excluded N = 79 randomised, 68 took medication Mean age 39 years (range 19 to 73) 94% Caucasian Median frequency of headaches 4 per month (range 2 to 30); 42/68 had ≤ 5 per month Baseline PI ≥ 4 (0 to 8); mean 6

NU2104 *(Continued)*

Interventions	Ibuprofen S(+) 200 mg, n = 68 Ibuprofen, racemic 400 mg, n = 68 Medication swallowed whole with full glass of water
Outcomes	PI: none to unbearable (0-8) PR: none to excellent (0-8) First noticeable relief PGE: poor to excellent (0-8) Adverse events
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated randomisation list"
Allocation concealment (selection bias)	Low risk	Remote packaging, numbered. Numbers allocated consecutively
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double dummy method
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double dummy method
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF or interpolation for missing data. Participants with missing or invalid baseline data excluded from eligible analysis
Size	High risk	< 50 participants per treatment arm (34)

Packman 2000

Methods	Randomised, double-blind, parallel groups, placebo- and active-controlled, single-dose study Single centre Assessment at 0, 30, 60 minutes, then hourly to 6 h
Participants	Episodic TTH (IHS criteria), ≥ moderate intensity, generally responded to OTC analgesics. Age >12 years, onset before age 50. Participants with recurrent (> 1 per month) migraine were excluded N = 154 Mean age 39 years M 37, F 117 Ethnic origin not reported Mean frequency 6 per month (range 4 to 15 [one participant])

Packman 2000 *(Continued)*

	Untreated headache duration: 2 to 4 h 84%, > 4 h 16% Baseline PI ≥ moderate
Interventions	Ibuprofen liquigel 400 mg, n = 60 Paracetamol 1000 mg, n = 62 Placebo, n = 32 Potential subjects reported to centre within 1 h of onset of ≥ moderate headache and were then randomised and treated if eligible
Outcomes	PI: none, mild, moderate, severe (0 to 3) PR: none, a little, some, a lot, complete (0 to 4) SPRID at 3 h and PRID at 2 and 3 h calculated Perceptible and meaningful relief AEs
Notes	Oxford Quality Score: R = 2, DB = 1, W = 1. Total = 4/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated code"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details of blinding not reported and medications were liquigels, caplets or placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details of blinding not reported and medications were liquigels, caplets or placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No withdrawals but imputation not mentioned
Size	High risk	< 50 participants per treatment arm (≤ 30)

Schachtel 1988

Methods	Randomised, double-blind, parallel groups, placebo-controlled, single-dose study Assessments over 2 h
Participants	TTH (Ad Hoc Committee criteria), ≥ 2 per month, with previous satisfactory relief from OTC analgesics N = 70 Mean age 21 years

Schachtel 1988 *(Continued)*

	M 36, F 34 Ethnic origin not reported Usual frequency of headaches not reported Baseline PI ≥ moderate (mean 63/100)
Interventions	Ibuprofen 400 mg, n = 35 Placebo, n = 35
Outcomes	PI: 100 mm VAS PR: 6 point categorical scale Discomfort of scalp muscles: 100 mm VAS Anxiety: 4 point categorical scale
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated randomization code"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"identical placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention of withdrawals or imputation (but only 2 h study)
Size	High risk	< 50 participants per treatment arm (35)

Schachtel 1996

Methods	Randomised, double-blind, parallel groups, placebo- and active-controlled, single-dose study Assessments at 0, 30, 60 minutes and 2, 3, 4 h
Participants	"Muscle contraction headache" (Ad Hoc Committee criteria), ≥ 2 per month, ≥ moderate severity, relieved by OTC analgesics. Age ≥ 18 years. Participants with history or symptoms of migraine were excluded N = 455 Mean age 22 years M 170, F 285

Schachtel 1996 *(Continued)*

	Ethnic origin not reported Usual frequency of headaches not reported Baseline PI ≥ moderate (mean 71/100 ± 10)
Interventions	Ibuprofen 400 mg, n = 153 Paracetamol 1000 mg, n = 151 Placebo, n = 151
Outcomes	PI: 100 mm VAS and 5-point Headache Pain Severity Score PR: no relief to complete relief (6-point categorical scale) SPID and TOTPAR at 4 h calculated Complete relief
Notes	Oxford Quality Score: R = 2, DB = 2, W = 1. Total = 5/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated randomization code"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identically appearing opaque capsules"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"identically appearing opaque capsules"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of imputation
Size	Unclear risk	50 to 199 participants per treatment arm (151 to 153)

van Gerven 1996

Methods	Randomised, double-blind, parallel groups, placebo- and active-controlled, single-dose study Assessments at 0, 15, 30, 45, 60, 90 minutes and 2, 3, 4 h
Participants	Episodic TTH (IHS criteria), ≥ moderate intensity, 4 to 24 episodes in previous 2 months, usually lasting ≥ 3 h, with satisfactory response to self-medicated analgesics. Participants with symptoms suggestive of migraine, chronic TTH, and cluster headache were excluded N = 162 (159 provided data) Mean age 39 years (range 21 to 73) M 50, F 109

van Gerven 1996 *(Continued)*

	Ethnic origin not reported Frequency in previous 2 months: 14 (range 4 to 28) 17% had "unspecified TTH" Baseline PI ≥ 25/100 ("moderate")
Interventions	Ibuprofen 200 mg, n = 40 Ketoprofen 25 mg, n = 39 Ketoprofen 50 mg, n = 40 Placebo, n = 39 Rescue medication allowed after 2 h
Outcomes	PI: 10 cm VAS (analysed as raw scores and as ratio of pretreatment value) Headache-free PR: 5-point categorical scale (strong worsening, slight worsening, no change, slight improvement, strong improvement) Use of rescue med Adverse events
Notes	Oxford Quality Score: R = 1, DB = 1, W = 1. Total = 3/5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details of randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Post remedication data considered missing, but did not state how handled
Size	High risk	< 50 participants per treatment arm (≤ 41)

BOCF: baseline observation carried forward; DB: double-blind; F: female; IHS: International Headache Society; LOCF: last observation carried forward; M: male; N: number of participants in study; n: number of participants in treatment arm; NSAID: non-steroidal anti-inflammatory drug; OTC: over-the-counter; PGE: Patient Global Evaluation; PI: pain intensity; PR: pain relief; R: randomised; SPID: sum of pain intensity difference; TOTPAR: total pain relief; TTH: tension-type headache; W: withdrawals

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
NCT01755702	Study terminated, no results

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT01464983

Methods	Randomised, double-blind (double-dummy), parallel groups, placebo- and active-controlled, single-dose study Assessments up to 4 h
Participants	Episodic TTH, mild or moderate in intensity. Age 18 to 65 years. Participants with migraine requiring medical treatment were excluded N = 1115 No further demographic details
Interventions	Ibuprofen 200 mg Ibuprofen 400 mg Aspirin 500 mg Aspirin 1000 mg Placebo
Outcomes	PR: categorical scale over 4 h Complete relief at 2 h Meaningful relief at 2 h PGE at 24 h Functional ability: 4-point categorical scale at 2 and 24 h Adverse events
Notes	Study completed (August 2004). No results posted

N: number of participants in study; PGE: Patient Global Evaluation; PR: pain relief; TTH: tension-type headache

Characteristics of ongoing studies *[ordered by study ID]*

NCT01842633

Trial name or title	Clinical study to evaluate efficacy of new paracetamol formulation compared to ibuprofen in headache
Methods	Randomised, double-blind (double-dummy), parallel groups, placebo- and active-controlled, single-dose study Assessments up to 4 h
Participants	Episodic TTH (IHS criteria), ≥ 2 per month of ≥ moderate severity. Age 18 to 65 years

NCT01842633 *(Continued)*	
	Estimated N = 300
	M and F
Interventions	Ibuprofen 400 mg
	Paracetamol 1000 mg + caffeine 130 mg
	Placebo
Outcomes	SPID, TOTPAR, SPRID at 1, 2, 3, 4 h
	PGE: very poor, poor, neutral, good, very good
	Time to perceptible and meaningful relief
	Use of rescue medication
Starting date	April 2013
Contact information	GlaxoSmithKline Clinical Trials
Notes	Estimated final data collection date for primary outcome: March 2015

F: female; M: male; N: number of participants in study; PGE: Patient Global Evaluation; SPID: sum of pain intensity difference; SPRID: sum of TOTPAR and SPID; TOTPAR: total pain relief; TTH: tension-type headache

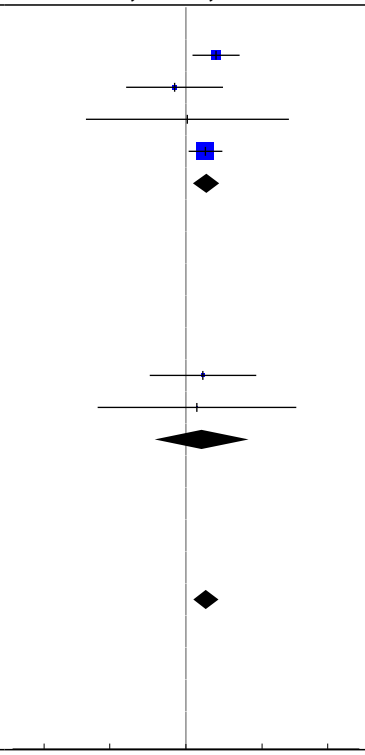
DATA AND ANALYSES

Comparison 1. ibuprofen 400 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 hours	4	1052	Risk Ratio (M-H, Random, 95% CI)	1.52 [1.17, 1.99]
1.1 Ibuprofen acid	4	839	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.16, 2.02]
1.2 Ibuprofen sodium	2	213	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.52, 3.76]
2 Pain-free at 1 hour	3	711	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.76, 2.92]
3 Patient Global Evaluation	3	739	Risk Difference (M-H, Random, 95% CI)	0.15 [0.09, 0.22]
4 Any adverse event	8	1645	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.64, 1.74]
5 Participants using rescue medication over 6 hours	2	589	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.42, 0.83]

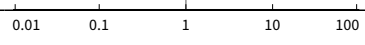
Analysis 1.1. Comparison 1 ibuprofen 400 mg versus placebo, Outcome 1 Pain-free at 2 hours.

Study or subgroup	Ibuprofen 400 mg n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Ibuprofen acid					
Kubitzek 2003	38/171	20/170		28.67%	1.89[1.15,3.11]
NCT01077973	12/80	4/21		6.78%	0.79[0.28,2.19]
NCT01362491	4/89	1/23		1.55%	1.03[0.12,8.81]
NL9701	83/191	27/94		55.76%	1.51[1.06,2.16]
Subtotal (95% CI)	**531**	**308**		**92.76%**	**1.54[1.16,2.02]**
Total events: 137 (Ibuprofen 400 mg), 52 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.44, df=3(P=0.49); I^2=0%					
Test for overall effect: Z=3.03(P=0)					
1.1.2 Ibuprofen sodium					
NCT01077973	17/79	3/20		5.62%	1.43[0.47,4.42]
NCT01362491	5/91	1/23		1.62%	1.26[0.16,10.3]
Subtotal (95% CI)	**170**	**43**		**7.24%**	**1.39[0.52,3.76]**
Total events: 22 (Ibuprofen 400 mg), 4 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%					
Test for overall effect: Z=0.66(P=0.51)					
Total (95% CI)	**701**	**351**		**100%**	**1.52[1.17,1.99]**
Total events: 159 (Ibuprofen 400 mg), 56 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.48, df=5(P=0.78); I^2=0%					
Test for overall effect: Z=3.1(P=0)					
Test for subgroup differences: Chi^2=0.03, df=1 (P=0.85), I^2=0%					



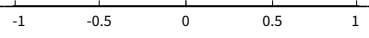
Analysis 1.2. Comparison 1 ibuprofen 400 mg versus placebo, Outcome 2 Pain-free at 1 hour.

Study or subgroup	Ibuprofen 400 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
NCT01077973	6/159	1/41		11.65%	1.55[0.19,12.5]
NCT01362491	0/180	0/46			Not estimable
NL9701	27/191	9/94		88.35%	1.48[0.72,3.01]
Total (95% CI)	**530**	**181**		**100%**	**1.48[0.76,2.92]**
Total events: 33 (Ibuprofen 400 mg), 10 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.97); I^2=0%					
Test for overall effect: Z=1.15(P=0.25)					



Analysis 1.3. Comparison 1 ibuprofen 400 mg versus placebo, Outcome 3 Patient Global Evaluation.

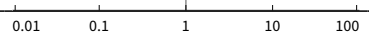
Study or subgroup	Ibuprofen 400 mg n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
Diamond 2000	24/99	8/48		23.84%	0.08[-0.06,0.21]
Kubitzek 2003	64/172	32/170		50.16%	0.18[0.09,0.28]
NL9701	88/172	27/78		26%	0.17[0.04,0.29]
Total (95% CI)	**443**	**296**		**100%**	**0.15[0.09,0.22]**
Total events: 176 (Ibuprofen 400 mg), 67 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.73, df=2(P=0.42); I^2=0%					
Test for overall effect: Z=4.56(P<0.0001)					



Favours placebo — Favours ibuprofen 400

Analysis 1.4. Comparison 1 ibuprofen 400 mg versus placebo, Outcome 4 Any adverse event.

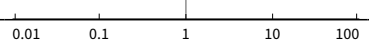
Study or subgroup	Ibuprofen 400 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Diamond 2000	15/105	3/55		13.63%	2.62[0.79,8.66]
Kubitzek 2003	4/151	7/153		24.06%	0.58[0.17,1.94]
NCT01077973	0/159	0/41			Not estimable
NCT01362491	0/180	0/46			Not estimable
NL9701	23/194	8/97		36.91%	1.44[0.67,3.09]
Packman 2000	0/60	4/32		20.21%	0.06[0,1.08]
Schachtel 1988	0/35	0/35			Not estimable
Schachtel 1996	0/151	1/151		5.19%	0.33[0.01,8.12]
Total (95% CI)	**1035**	**610**		**100%**	**1.06[0.64,1.74]**
Total events: 42 (Ibuprofen 400 mg), 23 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=8.07, df=4(P=0.09); I^2=50.41%					
Test for overall effect: Z=0.21(P=0.83)					



Favours ibuprofen 400 — Favours placebo

Analysis 1.5. Comparison 1 ibuprofen 400 mg versus placebo, Outcome 5 Participants using rescue medication over 6 hours.

Study or subgroup	Ibuprofen 400 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kubitzek 2003	25/151	45/153		63.71%	0.56[0.36,0.87]
NL9701	25/191	19/94		36.29%	0.65[0.38,1.11]
Total (95% CI)	**342**	**247**		**100%**	**0.59[0.42,0.83]**
Total events: 50 (Ibuprofen 400 mg), 64 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.16, df=1(P=0.69); I^2=0%					
Test for overall effect: Z=3.02(P=0)					



Favours ibuprofen 400 — Favours placebo

APPENDICES

Appendix 1. Search strategy for CENTRAL (via the Cochrane Library)

1. MeSH descriptor: [Ibuprofen] explode all trees (1191)
2. ibuprofen or Brufen or Advil or Motrin or Nurofen:ti,ab,kw (2477)
3. #1 or #2 (2477)
4. MeSH descriptor: [Headache] explode all trees (1603)
5. MeSH descriptor: [Headache Disorders] explode all trees (2064)
6. (headach* or cephalgi* or cephalalgi*):ti,ab,kw (12977)
7. #4 or #5 or #6 (13670)
8. #3 and #7 (173)

Limit to Trials 154

Appendix 2. Search strategy for MEDLINE (PubMed format)

1. Ibuprofen[mh] (6787)
2. (ibuprofen or Brufen or Advil or Motrin or Nurofen)[tiab] (9777)
3. 1 or 2 (10978)
4. Headache [mh] or Headache Disorders[mh] (46623)
5. (headach* or cephalgi* or cephalalgi*)[tiab] (61953)
6. 4 or 5 (82218)
7. 3 and 6
8. randomized controlled trial[pt] (380291)
9. controlled clinical trial[pt] (88378)
10. randomized[tiab] (334544)
11. placebo[tiab] (163234)
12. drug therap [sh] (1722919)
13. randomly[tiab] (226672)
14. trial[tiab] (380945)
15. groups[tiab] (1449869)
16. or 8-15 (3501658)
17. 3 and 7 and 16 (220)

Appendix 3. Search strategy for EMBASE (via Ovid)

1. ibuprofen.mp. (39384)
2. (ibuprofen or Brufen or Advil or Motrin or Nurofen).mp. (39429)
3. 1 or 2 (39429)
4. exp headache/ (145795)
5. exp "headache and facial pain"/ (213339)
6. (headach* or cephalgi* or cephalalgi*).mp. (193309)
7. 4 or 5 or 6 (230418)
8. random*.tw. (935791)
9. factorial*.tw. (24356)
10. crossover*.tw. (51349)
11. cross over*.tw. (23084)
12. cross-over*.tw. (23084)
13. placebo*.tw. (211565)
14. (doubl* adj blind*).tw. (152463)
15. assign*.tw. (251709)
16. allocat*.tw. (89095)
17. volunteer*.tw. (187269)
18. Crossover Procedure/ (41027)

19.Double-blind procedure/ (119377)
20.Randomized Controlled Trial/ (358449)
21.or 8-20 (1492240)
22.3 and 7 and 21 (816)

Appendix 4. Summary of outcomes in individual studies: efficacy

Study ID	Treatment	≤ Mild pain at 1 or 2 h	Pain-free at 1 h	Pain-free at 2 h	PGE (top two categories)	PID at 2 h
Diamond 2000	(1) Ibu 400 mg (2) Ibu 400 mg/Caff 200 mg (3) Caff 200 mg (4) Placebo	No data	No data	No data	v good or excellent (1) 24/99 (2) 37/97 (3) 11/57 (4) 8/48	No data
Kubitzek 2003	(1) Ibu 400 mg (2) Diclo K 12.5 mg (3) Diclo K 25 mg (4) Placebo	No data	No data	(1) 33/151 (2) 29/160 (3) 35/156 (4) 12/153	v good or excellent (1) 56/151 (2) 44/160 (3) 58/156 (4) 29/153	No usable data
Lange 1995	(1) Ibu 200 mg (2) Keto 12.5 mg (3) Keto 25 mg (4) Naprox 275 mg	No data	(1) 15/87 (2) 10/86 (3) 17/87 (4) 13/85	(1) 19/87 (2) 16/86 (3) 21/87 (4) 19/85	good or v good (1) 26/87 (2) 36/86 (3) 39/87 (4) 31/85	No usable data
Laveneziana 1996	(1) Ibu Arg (2) Pirox (3) Placebo Doses not reported	No data	No data	No data	complete or considerable (1) 10/26 (2) 8/26 (3) 4/26	No usable data
NCT01077973	(1) Ibu Na 400 mg (2) Ibu std 400 mg (3) Placebo	No data	(1) 5/79 (2) 1/80 (3) 1/41	(1) 17/79 (2) 12/80 (3) 7/41	No data	(1) 1.3 ± 0.7 (2) 1.2 ± 0.8 (3) 1.3 ±0.8
NCT01362491	(1) Ibu Na 400 mg (2) Ibu std 400 mg (3) Placebo	No data	(1) 0/91 (2) 0/89 (3) 0/46	(1) 5/91 (2) 4/89 (3) 1/46 Pain-free at 3 h	No data	(1) 1.0 ± 0.6 (2) 1.0 ± 0.5 (3) 0.4 ± 0.6

(Continued)

				(1) 34/91 (2) 34/89 (3) 4/46		
NL9701	(1) Ibu 400 mg (2) Paracet 1000 mg (3) Placebo	No data	(1) 27/191 (2) 32/188 (3) 9/94	(1) 83/191 (2) 87/188 (3) 27/94	(1) 88/172 (2) 84/176 (3) 27/78 "Evaluable population, not ITT"	(1) 1.24 ±0.96 (2) 1.35 ±0.9 (3) 0.91 ± 0.9
NU2104	(1) Ibuprofen S(+) 200 mg (2) Ibuprofen, racemic 400 mg,	No data	No data	No data	No data	No usable data
Packman 2000	(1) Ibu 400 mg (2) Paracet 1000 mg (3) Placebo	No data	No data	Pain-free at 3 h (1) 45/60 (2) 20/62 (3) 4/32	No data	No data
Schachtel 1988	(1) Ibu 400 mg (2) Placebo	No data	No data	No data	No data	(1) 43.7 ± 20.5 (2) 3.5 ± 8.2 (scale 1-100)
Schachtel 1996	(1) Ibu 400 mg (2) Para 1000 mg (3) Placebo	No data	No data	No data	No data	No data
van Gerven 1996	(1) Ibu 200 mg (2) Keto 25 mg (3) Keto 50 mg (4) Placebo	No data	No data	No data	No data	No data

Arg: arginine; Caff: caffeine; Diclo: diclofenac; Ibu: ibuprofen; Keto: ketoprofen; Na: sodium; Naprox: naproxen; Para: paracetamol; Pirox: piroxicam; std: standard tablet formulation

Appendix 5. Summary of outcomes in individual studies: adverse events, withdrawals, rescue medication

Study ID	Treatment	Any AE	Serious AE	AE withdrawals	Rescue medication
Diamond 2000	(1) Ibu 400 mg (2) Ibu 400 mg/Caff 200 mg (3) Caff 200 mg (4) Placebo	(1) 15/105 (2) 37/110 (3) 16/60 (4) 3/55	None	None	No data
Kubitzek 2003	(1) Ibu 400 mg (2) Diclo K 12.5 mg (3) Diclo K 25 mg (4) Placebo	(1) 4/151 (2) 6/160 (3) 4/156	None	None	Over 6 hr (1) 25/151 (2) 22/160 (3) 18/156

(Continued)

		(4) 7/153			(4) 45/153
Lange 1995	(1) Ibu 200 mg (2) Keto 12.5 mg (3) Keto 25 mg (4) Naprox 275 mg	No usable data	None	None	No data
Laveneziana 1996	(1) Ibu Arg (2) Pirox (3) Placebo Doses not reported	Nausea (1) 2/26 (2) 1/26	None	None	(1) 1/26 (2.75 h) (2) 1/26 (3.8 h)
NCT01077973	(1) Ibu Na 400 mg (2) Ibu std 400 mg (3) Placebo	None	None	None	No rescue medication used
NCT01362491	(1) Ibu Na 400 mg (2) Ibu std 400 mg (3) Placebo	None	None	None	No rescue medication used
NL9701	(1) Ibu 400 mg (2) Paracet 1000 mg (3) Placebo	(1) 23/194 (2) 22/190 (3) 8/97	None	None	Over 6 h (1) 25/191 (2) 18/188 (3) 19/94
NU2104	(1) Ibuprofen S(+) 200 mg (2) Ibuprofen, racemic 400 mg,	No data	None	None	No data
Packman 2000	(1) Ibu 400 mg (2) Paracet 1000 mg (3) Placebo	No AEs	None	None	No data
Schachtel 1988	(1) Ibu 400 mg(2) Placebo	No AEs	None	None	No data
Schachtel 1996	(1) Ibu 400 mg (2) Para 1000 mg (3) Placebo	(1) 0/153 (2) 0/151 (3) 1/151	None	None	No data
van Gerven 1996	(1) Ibu 200 mg (2) Keto 25 mg (3) Keto 50 mg (4) Placebo	(1) 3/40 (2) 2/39 (3) 7/40 (4) 2/39	None	None	At 2 h (1) 1/40 (2) 0/39 (3) 0/40 (4) 6/39

Arg: arginine; Caff: caffeine; Diclo: diclofenac; Ibu: ibuprofen; Keto: ketoprofen; Na: sodium; Naprox: naproxen; Para: paracetamol; Pirox: piroxicam; std: standard tablet formulation

WHAT'S NEW

Date	Event	Description
28 May 2019	Amended	Contact details updated.
11 October 2017	Review declared as stable	No new studies likely to change the conclusions are expected.

HISTORY

Protocol first published: Issue 1, 2015
Review first published: Issue 7, 2015

Date	Event	Description
3 May 2017	Review declared as stable	See Published notes.

CONTRIBUTIONS OF AUTHORS

All authors have participated in the writing of this review. RAM will be responsible for updating the review.

DECLARATIONS OF INTEREST

SD has no conflicts relating to this review or any similar product.

RAM has no conflicts relating to this review or any similar product.

PW has no conflicts relating to this review or any similar product.

LB has no conflicts relating to this review or any similar product.

For transparency, we acknowledge that we have received research support from charities, government, and industry sources at various times, but none relate to this review. We are funded by the NIHR for work on a series of reviews informing the unmet need of chronic pain relief and providing the evidence for treatments of pain but this review is not supported by that funding.

SOURCES OF SUPPORT

Internal sources

- The Oxford Pain Research Trust, UK.

  Institutional support

External sources

- No external source of support, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are no differences between protocol and review.

NOTES

In May 2017, this review was stabilised following discussion with the authors and editors. Restricted searches identified one new study (Packman 2015), but we judged that including it would not affect the conclusions of the review. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

Packman E, Leyva R, Kellstein D, Onset of analgesia with ibuprofen sodium in tension-type headache: a randomized trial. J Pharm Health Care Sci. 2015 Apr 2;1:13. doi: 10.1186/s40780-015-0012-9. eCollection 2015.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen; Administration, Oral; Analgesics, Non-Narcotic [*administration & dosage] [adverse effects]; Cyclooxygenase Inhibitors [therapeutic use]; Diclofenac [administration & dosage]; Ibuprofen [*administration & dosage] [adverse effects]; Ketoprofen [administration & dosage]; Naproxen [administration & dosage]; Numbers Needed To Treat; Pain Measurement; Piroxicam [administration & dosage]; Randomized Controlled Trials as Topic; Tension-Type Headache [*drug therapy]; Time Factors

MeSH check words

Adult; Humans